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To: FDA-Drug Alerts

Psychiatric News, American Psychiatric Association Newspaper

Re: Class labeling changes for SSRI/SNRI's regarding risk to newborns

I am writing to express my concern regarding the recommendation of the Pediatric Advisory Subcommittee of the Food and Drug Administration (FDA) to add class labeling for all SSRI/SNRI's within the pregnancy section and the dosage and administration section as described by Psychiatric News July 16, 2004 P33.

" Neonates exposed to SSRI/SNRI antidepressants late in the third trimester have developed AE(adverse events) requiring prolonged hospitalization, respiratory support, tube feeding. AE may arise immediately upon delivery."

Clinically that means that health care providers need to inform women of the risks to their neonate, which are presented as if they were facts for all SSRI/SNRI's when the actual data (studies that specify the need for prolonged hospitalization of newborns above the rate of what would be expected for an untreated depressed/anxious mother are not available). The large retrospective chart review study by Kallen, 2004 used presumable non-depressed, non anxious women as controls and contained no measure for level of depression and anxiety or actual medication compliance for pregnant women in the third trimester. They also did not specify if the respiratory distress was mild and transient or led to intensive treatment and prolonged hospitalization. There was no effect of SSRI's on hypoglycemia. Numbers of specific SSRI's were too small to determine differences between them. Even though Kallen reported on 106 women who were taking paroxetine they could not replicate the 21 % complications necessitating prolonged hospitalization in neonates exposed to paroxetine reported by Costei et al 2002. Overlander et al 2004 studying 46 SSRI exposed infants found only transient respiratory distress and hypotonia and no changes in developmental outcomes at 2 and 8 month of age. The careful prospective study by Hendrick et al, 2003 examining 131 birth outcomes for healthy nonsmoking women who took SSRIs during pregnancy and at delivery found neonatal complication at or below the national rate.

In the obstetric clinic at San Francisco General Hospital I have been treating over hundreds of women with SSRIs (predominantly sertraline, and more recently citalopram) up to delivery for the last 10 years and we had no case of an infant requiring prolonged hospitalization or treatment that could be attributed to the medication. In summary then all the research and clinical evidence points in the direction that SSRI treatment up to delivery is safe. Mild transient respiratory distress in some neonates exposed to SSRI's is likely but seems to be self limiting and does not justify the statement "requiring prolonged hospitalization"

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Case reports of serious reactions of neonates to paroxetine and Costei's finding need to be further investigated. This however does not warrant a generalized warning. Physicians being required to inform patients of this warning are likely to enhance women's stress and anxiety at a crucial time of their pregnancy. In addition the labeling does not require physicians to warn patients about the substantial and well documented risk of relapse into depression in the mother if she stops the medication (Cohen et al, 2004 and Wisner et al, 2004). Increased stress also can affect the intrauterine and neonatal environment in potentially negative ways.

RE: Changes under administration section of labeling : Physicians will be advised to taper dosage of the SSRIs during the last trimester, so women are medication free for 7-10 days prior to delivery."

Neonatal outcome: To my knowledge there is no study in the literature that compares neonatal outcomes in women who did or did not taper their medication prior to delivery. Costei et al, 2003 does compare first trimester and last trimester exposure to paroxetine and found neonatal effects after third trimester exposure, but the results were not replicated in other studies and they only pertain to paroxetine. If serious withdrawal symptoms do occur, such as seizures, intracranial hemorrhage (Salvia-Roiges et al 2003) would they not pose an increased risk in utero?. If SSRI exposed neonates do suffer either a CNS serotonergic overstimulation or withdrawal symptoms as indicated by the studies by Laine et al, 2003 and Nordeng et al 2001, the effects were reported to be transient and mild. Acknowledging the risk for neonates and wholeheartedly endorsing close follow up of exposed neonates, the consensus of clinician working in this area is still that it is the safest course of action to continue the medication. (Koren 2004, Patkar et al 2004, Hendrick et al 2003, Altshuler et al 2001)

Maternal outcome: The second major difficulty with the discontinuation of SSRI's is of course the interruption of necessary treatment of the mother. Anxiety and depressive symptoms often intensify the 4 weeks prior to delivery and mother and fetus would be exposed to increases in stress hormones at a vulnerable time. In addition if the mother is medication free 2 weeks prior to delivery she has no protection against postpartum depression and anxiety for the first 2-3 weeks postpartum since it would take that amount of time to achieve a therapeutic antidepressant level even if the medication is restarted after birth. Because of the well established risk for relapse and the serious consequences of a major depressive episodes for the mother and her newborn the risk benefit analysis favors continuation of the medication. This risk and benefit analysis is not addressed in the communication to the prescribing physicians and there is no registry to monitor negative outcomes after discontinuation of antidepressant medication in pregnant women.

Action requested: For those SSRI's (like sertraline) where labeling changes have not been agreed upon I strongly urge not to add to the already faulty labeling information.

For sertraline:" Pregnancy category C: There are no adequate and well controlled studies in pregnant women." This statement does not correspond to the multiple well controlled studies demonstrating no teratogenic effects in humans and no significant clinical effect on delivery outcome.

Nursing Mothers-"It is not known whether sertraline or its metabolites are excreted in human milk." Again it is known and by Expert Consensus Guidelines sertraline is recommended for breast-feeding mothers if an SSRI is required.

To add further warnings that are contradicted by clinical studies such as "the adverse effects in neonates including prolonged hospitalization" encourages dangerous practices for physicians who do not have the opportunity to study the literature in depth. This ultimately jeopardizes patient care in a significant way.

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